19 ~~38~~. An apparatus according to claim ~~36~~ 17 wherein said spacer is a conductive oligomer.

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20 ~~39~~. An apparatus according to claim ~~35~~ 16 wherein said passivation agent monolayer comprises conductive oligomers.

21 ~~40~~. An apparatus according to claim ~~35~~ 16 wherein said passivation agent monolayer comprises insulators.--

REMARKS

Claims 19-31 and 33-40 are pending. Support for new claims 35-40 is found within the specification on page 32, lines 21-22 and on page 35, lines 9-17, as well as within the claims.

As a preliminary matter, the applicants note that a new declaration is included, reflecting a change in priority back to November 6, 1996. In addition, the Examiner is respectfully requested to acknowledge the U.S. patent applications cited first in the Information Disclosure Statement filed January 23, 1998, and recited with the Supplemental Information Disclosure Statement filed herewith.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 19-25 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner objects to the double use of "covalently attached" in claims 19 and 20. Claim 19 has been amended to clarify that the nucleic acid is attached to the electrode

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via a spacer, and claim 20 has been amended to clarify that there are two distinct attachments. This amendment should obviate the rejection.

The Examiner objects to claim 26 and dependent claims 27-34 because it is unclear to what the electron transfer moiety is attached. Claim 26 has been amended and this amendment should obviate the rejection.

The Examiner objects to the use of "R is a substitution group" in claim 31 because there is not a standard chemical definition of "a substitution group" in the claim or in the specification. The applicants respectfully remind the Examiner that an inventor can be his own lexicographer, defining terms as he wishes. See Intellicall, Inc. v. Phonometrics, Inc., 21 USPQ 2d 1383 (Fed. Cir. 1992).

Applicants respectfully point out that suitable substitution groups for R are defined in the specification beginning on page 13, line 19 through page 16, line 3:

> The aromatic group may be substituted with a substitution group, generally depicted herein as R. R groups may be added as necessary to affect the packing of the conductive oligomers, i.e. when the nucleic acids attached to the conductive oligomers form a monolayer on the electrode, R groups may be used to alter the association of the oligomers in the monolayer. R groups may also be added to 1) alter the solubility of the oligomer or of compositions containing the oligomers; 2) alter the conjugation or electrochemical potential of the system; and 3) alter the charge or characteristics at the surface of the monolayer.
>
> In a preferred embodiment, when the conductive oligomer is greater than three subunits, R groups are preferred to increase solubility when solution synthesis is done. However, the R groups, and their positions, are chosen to minimally effect the packing of the conductive oligomers on a surface, particularly within a monolayer, as described below. In general, only small R groups are used within the monolayer, with larger R groups generally above the surface of the monolayer. Thus for example the attachment of methyl groups to the portion of the conductive oligomer within the monolayer to increase solubility is preferred, with attachment of longer alkoxy groups, for example, C3 to C10, is preferably done above the monolayer surface. In general, for the systems described herein, this generally means that attachment of sterically significant R groups is not done on any of the first three oligomer subunits, depending on the length of the insulator molecules.

Suitable R groups include, but are not limited to, hydrogen, alkyl, alcohol, aromatic, amino, amido, nitro, ethers, esters, aldehydes, sulfonyl, silicon moieties, halogens, sulfur containing moieties, phosphorus containing moieties, and ethylene glycols. In the structures depicted herein, R is hydrogen when the position is unsubstituted. It should be noted that some positions may allow two substitution groups, R and R', in which case the R and R' groups may be either the same or different.

By "alkyl group" or grammatical equivalents herein is meant a straight or branched chain alkyl group, with straight chain alkyl groups being preferred. If branched, it may be branched at one or more positions, and unless specified, at any position. The alkyl group may range from about 1 to about 30 carbon atoms (C1 -C30), with a preferred embodiment utilizing from about 1 to about 20 carbon atoms (C1 -C20), with about C1 through about C12 to about C15 being preferred, and C1 to C5 being particularly preferred, although in some embodiments the alkyl group may be much larger. Also included within the definition of an alkyl group are cycloalkyl groups such as C5 and C6 rings, and heterocyclic rings with nitrogen, oxygen, sulfur or phosphorus. Alkyl also includes heteroalkyl, with heteroatoms of sulfur, oxygen, nitrogen, and silicone being preferred. Alkyl includes substituted alkyl groups. By "a substituted alkyl group" herein is meant an alkyl group further comprising one or more substitution moieties "R", as defined above.

By "amino groups" or grammatical equivalents herein is meant $-NH_2$, -NHR and $-NR_2$ groups, with R being as defined herein.

By "nitro group" herein is meant an $-NO_2$ group.

By "sulfur containing moieties" herein is meant compounds containing sulfur atoms, including but not limited to, thia-, thio-and sulfo-compounds, thiols (-SH and -SR), and sulfides (-RSR-). By "phosphorus containing moieties" herein is meant compounds containing phosphorus, including, but not limited to, phosphines and phosphates. By "silicon containing moieties" herein is meant compounds containing silicon.

By "ether" herein is meant an -O-R group. Preferred ethers include alkoxy groups, with $-O-(CH_2)_2CH_3$ and $-O-(CH_2)_4CH_3$ being preferred.

By "ester" herein is meant a -COOR group.

By "halogen" herein is meant bromine, iodine, chlorine, or fluorine. Preferred substituted alkyls are partially or fully halogenated alkyls such as CF_3, etc.

By "aldehyde" herein is meant -RCOH groups.

By "alcohol" herein is meant -OH groups, and alkyl alcohols -ROH.

By "amido" herein is meant -RCONH-or RCONR-groups.

By "ethylene glycol" herein is meant a $-(O-CH_2-CH_2)_n-$group, although each carbon atom of the ethylene group may also be singly or doubly substituted, i.e. $-(O-CR_2-CR_2)_n-$, with R as described above. Ethylene glycol derivatives with other heteroatoms in place of oxygen (i.e. $-(N-CH_2-CH_2)_n-$or $-(S-CH_2-CH_2)_n-$, or with substitution groups) are also preferred.

Preferred substitution groups include, but are not limited to, methyl, ethyl, propyl, alkoxy groups such as $-O-(CH_2)_2CH_3$ and $-O-(CH_2)_4CH_3$ and ethylene glycol and derivatives thereof.

Accordingly, the applicants submit that the term "R is a substitution group" is sufficiently defined and the rejection under 35 §112, second paragraph should be withdrawn.

Rejection under 35 U.S.C. §102(e)

Claims 19-25 are rejected under 35 U.S.C. §102(e) as being anticipated by Ribi et al., (the '568 patent).

By way of summary, the present invention is directed to compositions and methods useful in the detection of nucleic acids utilizing electron transfer mechanisms. The invention relies on electron transfer between an electron donor and acceptor groups (electron transfer moieties or ETMs) present in a nucleic acid hybridization complex and an electrode. Thus, the invention utilizes an electrode with a covalently attached nucleic acid. Upon hybridization with a target sequence, double-stranded nucleic acid hybridization complex forms that contains an ETM, and detection proceed with the input of an AC signal resulting in electron transfer between the ETM and the electrode.

It should be noted that the conductivity or redox state of the spacer used to connect the nucleic acid and the electrode (i.e. either a conductive oligomer or an insulator) does not change during the assay.

In contrast, Ribi et al. describes a system that utilizes at least four components: a substrate, a set of interdigitating electrodes, a polymerizable surfactant film that forms a crystalline structure, and at least one binding ligand ("a member of a specific binding pair").

Ribi's substrate is an insulative solid support (see column 3, line 19), and can be made of a variety of materials. Preferred embodiments utilize polystyrene (see column 4, line 36). It should be noted that polystyrene is not a conductive material, and is not used in Ribi et al. as such.

A "highly oriented polymerized surfactant film" (column 3, lines 19-20) is then added to the insulative substrate. This may be done covalently or non-covalently (see column 3, lines 37-41). This surfactant film is either electronically semi-conducting or variably conducting (see column 3, lines 21-22).

Binding members (i.e. for binding a target analyte) are then added to the surfactant film (sometimes also referred to in Ribi et al. as a lipid portion; see column 5, line 26). The binding members are generally added to the surfactant film by using a linker (see column 5, lines 25-56). These linkers are chosen depending on the "degree to which one wishes to perturb the electrical properties of the polymer" (see column 5, line 34-36). That is, as shown below, the mechanism of Ribi et al. relies on a change in the electromagnetic properties of the film as a result of the binding of a target analyte. Thus, Ribi et al. states that "[t]he more rigid and shorter the linker, assuming high affinity analyte binding, the greater the perturbation of the polymer upon binding of the specific binding member to its complementary member." (Column 5, lines 37-40).

In addition, this perturbation causes a change in the electrical properties of the surfactant due to the presence of dopants. These dopants (donors and acceptors) alter their

orientation in response to the binding of the target analytes, thus causing the changes in the electrical properties of the film. See column 5, lines 59-64:

> The orientation of the acceptor or donor molecule (dopant) with respect to the polymer lattice will affect the polymers' net electrical characteristics. The electrical properties of the film will be affected by analyte binding where the binding event causes a change in the orientation of the dopant molecule.

Generally, Ribi et al. appears to function in the following way. Upon binding of a target analyte, the electromagnetic properties of the film change (either its electronic or optical properties; see column 3, line 26) as a result of binding of a target analyte for detection. Therefore the film is the intervening medium between the two electrodes, and changes in the film's properties serve as the basis of the assay for the presence or absence of the target analyte.

Furthermore, in order to make this work (as shown in Figure 3, column 16, lines 27-31, and column 16, line 61 to column 17, line 42 ("Electrode Protection") of Ribi et al.), the electrodes must be electrically insulated from the aqueous medium using such things as parafilm, wax, nail polish, etc., so that direct electrical contact of two interdigitating electrodes does not occur. As the Examiner will appreciate, if there is direct electrical contact of the two electrodes through the aqueous media, the presence of charge carriers in the sample would provide two pathways for current flow: through the solution and through the film. Presumably this would be unacceptable.

As argued previously, Ribi et al. does not outline covalent attachment of nucleic acids to the electrode. The Examiner states that "the claims are not limited to covalent attachment of electrode to nucleic acid". However, the applicants respectfully disagree. In each independent claim the nucleic acid is covalently attached: claim 19 states that the "electrode comprises a single stranded nucleic acid covalent attached to said electrode via a spacer"; claim 20 recites that the "electrode comprises a covalently attached single stranded nucleic acid"; and claim 26 recites that the "electrode comprises a covalently attached first single stranded nucleic acid".

In addition, the claims as amended further recite that the electrodes comprise passivation agent monolayers. Clearly, the compositions of Ribi et al. do not have monolayers.

As the Examiner is aware, the law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. SSIH

Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

Ribi et al. does not disclose either the covalent attachment of nucleic acids to the electrode or the use of monolayers. Accordingly, the rejection is improper and should be withdrawn.

Rejection under 35 U.S.C. §103

Claims 19-34 are rejected under 35 U.S.C. §103 as being obvious over Ribi et al.

As stated in M.P.E.P. §2142, a *prima facie* case of obviousness requires three basic criteria to be met. First, there must be some suggestion or motivation to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, taken alone or in combination, must teach or suggest all the claim limitations.

The applicants submit that Ribi does not provide any motivation or suggestion to practice the claimed invention. There simply is no motivation to covalently attach the nucleic acids to the electrode. In fact, Ribi et al. actually teaches away from this, as it is important to the Ribi invention that the electrodes must be electrically insulated from the aqueous medium containing the target analyte for binding to the binding member. Having the binding member directly on the electrode would not allow this electrical insulation. Thus Ribi actually teaches away from practicing the invention. As stated in M.P.E.P. §2143.01:

> If [the] proposed modification would render the prior art invention being modified unstatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 221 USPQ 1125 (Fed. Cir. 1984). Similarly, a reference which leads one of ordinary skill in the art away from the

claimed invention cannot render the claimed invention unpatentably obvious. Dow Chemical Co. v. American Cyanamid Co., 2 USPQ 2d 1350 (Fed. Cir. 1987).

Therefore, Ribi et al. does not provide the required motivation to combine. Thus a *prima facie* case of obviousness has not been made and the rejection is improper.

Even assuming, arguendo, that the required motivation exists, Ribi et al. does not provide a reasonable expectation of success. As argued above, the attachment of the nucleic acid to the electrode does not give a reasonable expectation of success. Accordingly, a *prima facie* case of obviousness has not been made and the rejection is improper.

Finally, Ribi et al. does not teach or suggest all of the claim elements, including the covalent attachment of the nucleic acid to the electrode. Accordingly, a *prima facie* case of obviousness has not been made and the rejection is improper.

Accordingly, the rejection under 35 U.S.C. §103 should be withdrawn.

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels that there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

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APPENDIX OF PENDING CLAIMS

19. (Twice Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second [measuring] electrode, wherein said first [measuring] electrode comprises a single stranded nucleic acid covalently attached to said electrode via a spacer, wherein said electrode further comprises a passivation agent monolayer [conductive oligomer, wherein said conductive oligomer is also covalently attached to a single stranded nucleic acid]; and

b) an AC/DC voltage source electrically connected to said test chamber.

20. (Twice Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second [measuring] electrode, wherein said first [measuring] electrode comprises a covalently attached single stranded nucleic acid, wherein said electrode further comprises a passivation agent monolayer and wherein said nucleic acid further comprises a covalently attached second electron transfer moiety; and

b) an AC/DC voltage source electrically connected to said test chamber.

21. An apparatus according to claim 19, [or] 20 or 26, further comprising:

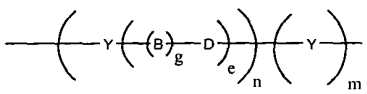
d) a processor coupled to said electrodes.

22. (Amended) An apparatus according to claim 19, [or] 20 or 26, wherein said AC voltage source is capable of delivering frequencies from between about 1 Hz to about 100 kHz.

23. (Twice Amended) An apparatus according to claim 20, wherein said single stranded nucleic acid[s are] is covalently attached to said first [measuring] electrode via a spacer.

24. An apparatus according to claim 23, wherein said spacer is a conductive oligomer.

25. (Twice Amended) An apparatus according to claim 19, 23 [24] or 27 [28], wherein said spacer is a conductive oligomer [has] having the formula:



wherein

Y is an aromatic group;

n is an integer from 1 to 50;

g is either 1 or zero;

e is an integer from zero to 10; and

m is zero or 1;

wherein when g is 1, B-D comprises two atoms forming a bond able to conjugate with neighboring bonds; and

wherein when g is zero, e is 1 and D is selected from the group consisting of carbonyl and a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen and phosphorus.

26. (Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second [measuring] electrode, wherein said first [measuring] electrode comprises a covalently attached first single stranded nucleic acid and a passivation agent monolayer;

b) a second nucleic acid [comprising a] covalently attached to a electron transfer moiety; and

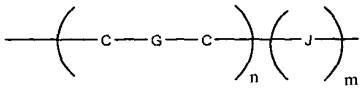
c) an AC/DC voltage source electrically connected to said test chamber.

27. (Amended) An apparatus according to claim 26 wherein said single stranded nucleic acid[s are] is covalently attached to said electrode via a spacer.

28. An apparatus according to claim 27, wherein said spacer is a conductive oligomer.

29. An apparatus according to claim 27, wherein said spacer is an insulator.

30. (Amended) An apparatus according to claim 19, 23 [24] or 27 [28], wherein said spacer is a conductive oligomer having [has] the formula:



wherein

C are carbon atoms;

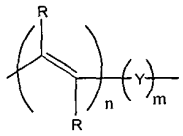
n is an integer from 1 to 50;

m is 0 or 1;

J is a heteroatom selected from the group consisting of nitrogen, silicon, phosphorus, sulfur, carbonyl and sulfoxide; and

G is a bond selected from single, double and triple bonds.

31. (Amended) An apparatus according to claim 19, 23 [24] or 27 [28], wherein said spacer is a conductive oligomer having [has] the formula:



wherein

n is an integer from 1 to 50;

m is either zero or 1;

Y is an aromatic group; and

R is a substitution group.

33. (Amended) An apparatus according to claim 19, 20 or 26 [32] wherein said passivation agent monolayer comprises conductive oligomers.

34. (Amended) An apparatus according to claim 19, 20 or 26 [32] wherein said passivation agent monolayer comprises insulators.